Remarks

Claims 1 through 8 are pending in this case. Pending claims 1 through 8 have been cancelled. New claims 9 through 14 have been added.

Applicants discovered a stable preformulation form of activated protein C (aPC), providing for aPC cryogranules, a process for preparing aPC cryogranules, and a process of preparing an aPC lyophilized formulation from the aPC cryogranules. This invention provides one means of processing commercial scale aPC suitable for storage, handling, and recovery.

On March 24, 2004, a telephone interview concerning this case was conducted between the Examiner and the Attorney for Applicants. The Interview Summary provided by the Examiner fairly reflects the substance of the interview with following exceptions:

1) A declaration will be provided by one of the Applicants.
2) The declaration will detail the differences between cryogranulation and lyophilization.
3) The declaration will show that cryogranulation of aPC is different and not predictable from cryogranulation of other proteins.
4) The Examiner views Claims 5 and 6 as process claims for the activated protein C product. As such, the Examiner prefers that these claims be amended to a product-by-process format. Attorney for Applicants agrees to consider these amendments.

REJECTION OF CLAIMS 42 AND 43 UNDER 35 U.S.C. § 102(b)

Claims 5 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Foster *et al.* (U.S. Patent No. 5,516,650). The Examiner indicated in the telephone interview conducted on March 24, 2004 that Claims 5 and 6 are process claims for the activated protein C (aPC) product. As such, the Examiner preferred that these claims be amended to a product-by-process format. Attorney for Applicants agreed to these consider these amendments. According to *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted), "[E]ven though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by process claim is the same as or obvious from a product of the prior art, the claim is unpatentable event though the prior product was made by a different process." A

subsequent telephone call to the Examiner discussing this point resulted in a determination that the Examiner continued to not view Claims 5 and 6 as allowable in their current format and still requested amendment of these claims to a product-by process format. While Applicants do not acquiesce to the merits of the Examiner's rejection, Applicants have cancelled Claims 5 and 6. Furthermore, Applicants reserve the right to pursue the subject matter of cancelled Claims 5 and 6 by filing a continuation case. In view of these points, Applicants respectfully request withdrawal of this rejection.

REJECTION OF CLAIMS 1-8 UNDER 35 U.S.C. § 103(a)

Claims 1 through 8 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tse *et al.* (U.S. Patent No. 5,716,645; the '645 patent) taken with Foster *et al.* (U.S. Patent No. 5,516,650; the '650 patent). Applicants wish to direct the Examiner's attention to the fact that Claims 1 through 8 have been cancelled and replaced with new Claims 9 through 14. Applicants respectfully assert that the Examiner has failed to set forth a *prima facie* case of obviousness and request withdrawal of this rejection.

In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the court defined the test for determining obviousness under 35 U.S.C. § 103: 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. The USPTO bears the burden of establishing a *prima facie* case. (*In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984)). In order to establish a *prima facie* case, the Examiner must show 1) some suggestion or motivation to modify the reference or to combine reference teachings (*In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988)); 2) the proposed modification had a reasonable expectation of success by a skilled artisan at the time of the invention (*Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991)); and 3) the prior art reference or combination of references must teach or suggest all limitations of the claims (*In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness.

Applicants discovered one means for providing a stable preformulation form of aPC that would facilitate handling large volumes and maintain product integrity of the solution during the manufacturing process. The '645 patent, on the other hand, teaches the use of plasma that is cryoprecipitated, not cryogranulated, and then used to prepare a fibrinogen composition essentially free of Factor VIII. Furthermore, the Examiner notes that

the '645 patent does not mention aPC. However, the Examiner then states that "[t]he activated fibrinogen and FVIII [Factor VIII] include the specific activated protein C since they are generic."

In the attached declaration, Dr. Jeffrey C. Baker indicates that activated protein C is quite different from plasma, fibrinogen, and Factor VIII. He states that the percent sequence identity between human protein C and fibrinogen as well as between human protein C and Factor VIII is low. Additionally, plasma contains a variety of proteins, making it even more markedly different from activated protein C. Furthermore, activated protein C has distinct post-translational modifications – including addition of oligosaccharides onto four *Asn*-glycosylation sites – and a particularized glycosylation pattern – for example, contains *N*-acetylgalactosamine (GalNAc) in its Asn-linked oligosaccharides – that further distinguish it from the proteins in the '645 patent (Yan *et al.*, *Glycobiology*, 3: 597-608 (1993)).

It is important to note that the '645 patent is directed to cryoprecipitation, a purification technique used to facilitate the separation of a solid from a liquid, not cryogranulation. Dr. Baker, in the attached declaration, further states that even if the '645 patent included teachings on cryogranulation, cryogranulation of other protein products does not suggest the viability of using cryogranulation as a processing technique for activated protein C. For any freezing methodology, various issues must be addressed, including the effect of freezing rate on product stability (Ryan *et al.*, *BioPharm*, 32-38 (1995)). Ryan *et al.* reported on the physical attributes of cryogranulated cell pastes and inclusion body pastes derived from fermentation of *E. coli* producing recombinant human proteins, not their product stability. However, Schmidt *et al.* reported that a wide variety of cryogranulated molecules, including a tripeptide, a small protein (approximately 6,000 MW), a large protein (>60,000 MW), an enzyme intermediate, and vancomycin hydrochloride, showed excellent stability (Schmidt *et al.*, (1997)). Dr. Baker indicates that such a conclusion was available only after performing the experiments on each of the molecules. In fact, Schmidt *et al.* notes that "[a]s the era of biotechnology continues to advance, new technologies such as cryogranulation must be developed and implemented to facilitate the processing of reactive biomolecules from the bulk stage to the finished product dosage form while maintaining stability, purity, and other quality attributes." (*Id.*). Dr. Baker further comments that in the absence of experimentation, the activity and stability of a protein subjected to any freezing technique, including cryogranulation conditions, cannot be predicted. With any protein, but

particularly proteins used for pharmaceutical products, experimentation is necessary to ascertain whether or not a particular protein's activity is retained and recovered at a level sufficient to maintain commercial utility. As such, the flash freezing technique employed in cryogranulation can have unique effects on different proteins and must be tested on a given protein in order to determine whether or not cryogranulation is a feasible processing technique. Therefore, successfully using cryogranulation for activated protein C is not predictable from use of this technique for other protein products. Given the lack of cryogranulation teachings in the '645 patent as well as the marked distinctions between different proteins' response to cryogranulation and between aPC and the proteins noted in the '645 patent, Applicants respectfully assert that the '645 patent's teachings do not render the claims of the present invention obvious.

Next, the Examiner addresses the process of preparing a lyophilized formulation of aPC after the addition of a pharmaceutically acceptable bulking agent. The Examiner directs his objections on this issue to Claims 1 through 8. Applicants respectfully assert that only Claims 7 and 8 involve a process of preparing a lyophilized formulation of aPC after thawing aPC cryogranules. Applicants wish to direct the Examiner's attention to the fact that Claims 7 and 8 have been cancelled and replaced with new Claims 10 through 12. For each claim, the process still includes thawing the aPC cryogranules to form a solution before proceeding to remaining steps.

While the '645 patent employs lyophilization for fibrinogen and the '650 patent involves the use of stabilizers with protein C or aPC and subsequent lyophilization, neither reference teaches the cryogranulation of aPC or thawing aPC cryogranules to form a solution before lyophilization with or without the addition of a pharmaceutically acceptable bulking agent. Plus, as previously noted, the '645 patent is directed to cryoprecipitation only, not cryogranulation. Nevertheless, it is important to note the differences between cryogranulation and lyophilization. In the attached declaration, Dr. Baker details these differences. He states that cryogranulation and lyophilization are two distinct processing techniques, differing in a variety ways. For example, the end product produced using cryogranulation is a frozen liquid containing both the desired product and water in the form of discrete granules from solutions or slurries of bulk drug substances after contact with a cryogenic material such as liquid nitrogen (Schmidt *et al.*, *BioPharm*, 28-32 (1997)). Alternatively, lyophilization extracts the water from the product, leaving a readily handled solid product plug. Lyophilization is also referred to as freeze drying since it involves the

process of isolating a solid substance from solution by freezing the solution and evaporating the ice under vacuum (see http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=lyophilization&action=Search+OMD).

Dr. Baker also notes that the physical nature of the product differs given the technique used. Cryogranules are frozen pellets that can roll, spill, or break. On the other hand, lyophilized products are solid powders that can flow, cake, or be milled. Various temperatures affect cryogranulated products. At high temperatures, cryogranulated products boil. Cryogranules transform into a liquid at room temperature, but remain frozen solids at the proper cold temperature. Alternatively, lyophilized products are solid at any temperature.

According to Dr. Baker, chemical stability is linked to different factors for cryogranulated products and lyophilized products. Cryogranulated products have uniform hydration, with their chemical stability linked to temperature. While most of the water is removed from lyophilized products, trace amounts of water can remain. The degree of hydration can vary between products and between production lots of the same product. Thus, chemical stability is linked to hydration for lyophilized products.

Furthermore, the process for preparing cryogranules and lyophilized products are quite different. Cryogranules are generated by contacting droplets of the solution containing the product in liquid nitrogen or other freezing agents suitable for rapidly freezing the solution at temperatures from –40°C to –90°C (Schmidt *et al.*, (1997)). Discrete frozen pellets are produced during the residence time in which the solution is in contact with liquid nitrogen (*Id.*). As such, cryogranulation is a partitioning technique, where the product is merely divided into small frozen units. Alternatively, lyophilization is the process of isolating a solid substance from solution by freezing the solution and sublimating the ice under vacuum, as noted above (see http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=lyophilization&action=Search+OMD). Thus, lyophilization is a separation technique, where the product is separated as a solid from the liquid.

All of these points support the assertion that cryogranulation of aPC differs from lyophilization of aPC. Furthermore, cryogranulation of aPC is not taught by the cited references. For the subject matter of this application, aPC cryogranules are a precursor to preparing a lyophilized formulation of aPC. As such, neither the '645 patent nor the '650 patent, alone or in combination, direct the skilled artisan to the claims of the present invention.

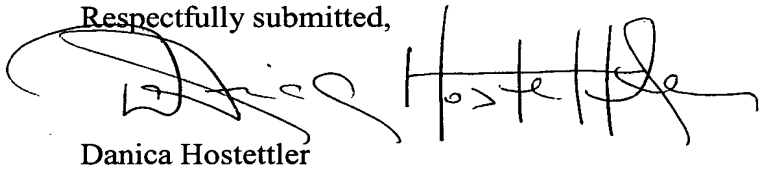
No evidence exists of any suggestion or motivation to modify or combine teachings from the '645 patent or the '650 patent in order to arrive at Applicants' present invention. Additionally, neither the '645 patent nor the '650 patent teach or suggest all limitations of the claims. Without any teachings involving cryogranulation of aPC, these references are completely unable to direct the skilled artisan to this invention. As such, these references do not render Applicants' present invention obvious. For the above-stated reasons, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants assert that the above-stated remarks obviate the noted rejections. While Applicants do not acquiesce to the merits of the Examiner's rejection, Applicants have cancelled original Claims 5 and 6, thereby overcoming the anticipation rejection. This invention is not obvious since neither the '645 patent nor the '650 patent involves cryogranulation of aPC and no suggestion or motivation to modify or combine teachings from the '645 patent or the '650 patent exists.

In view of these points, Applicants courteously solicit reconsideration of these rejections and passage of this case to issuance.

Respectfully submitted,



Danica Hostettler
Attorney for Applicants
Registration No. 51,820
Phone: 317-276-3711

Eli Lilly and Company
Patent Division/DH
P.O. Box 6288
Indianapolis, Indiana 46206-6288

May 18, 2004